Original Article

Prevalence of Subclinical Atrial Fibrillation Detected by Cardiac Implantable Electronic Device and Its Association with Ischemic Stroke: A Single-Center Study

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Background: Atrial fibrillation (AF), whether paroxysmal or persistent, can cause stroke and mortality and impact on the quality of life. These days, permanent pacemakers can provide intracardiac electrograms; any tachyarrhythmias detected are reported as atrial high-rate events (AHRE), which could lead to the identification of subclinical AF. However, there are still no data on the prevalence of AHRE or on their correlation with stroke in the Thai population.

Objective: The primary and secondary outcomes were to evaluate the prevalence of AHRE in patients who underwent cardiac implantable electronic device (CIED) surgery in the Thai population, and the correlation of AHRE with stroke, respectively.

Materials and Methods: The authors conducted a retrospective, cohort, descriptive study on patients who had undergone a dual-chamber CIED implantation during a 7-year period, with a median follow-up of 5.8 years.

Results: One hundred ninety-six patients who had undergone a dual-chamber CIED implantation and been followed up for 5.8 years were retrospectively reviewed. In the case of the primary outcome, AHRE were detected in 82 of the patients (41.8%). As to the secondary outcomes, 20 patients (10.2%) were lost to follow-up during the study period. Stroke occurred in five out of the 78 patients in the AHRE group (6.4%), whereas stroke occurred in one out of the 98 patients in the non-AHRE group (1.0%); however, there was no statistically significant difference (p=0.089) between the two groups. The mortality rates of the AHRE and non-AHRE groups were also nearly equal (23.4% vs. 23.5%; p=0.989).

Conclusion: The present study examined AHRE, which were assumed to be indicative of subclinical AF. They were found in a sizeable proportion (41.8%) of the Thai study population who had been implanted with a dual-chamber CIED. No statistically significant association was found between AHRE and either stroke or the mortality rate.

Keywords: CIED, Atrial fibrillation, Prevalence

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Atrial fibrillation (AF) is one of the most common cardiac arrhythmias, occurring in 1% to 2% of the general population. The life-time risk for developing AF in adults older than 40 years is nearly 20%[1]. The consequences of AF include a degraded quality of life and increased mortality and stroke rates[2]. However, AF is diagnosed less than its actual incidence. This is because this form of arrhythmia may be paroxysmal in nature and it may not have any symptoms. Paroxysmal AF represents 25% to 62% of all AF diagnoses[3].

Hohnloser et al reported the same stroke risk rates for paroxysmal and persistent AF[4]. However, the important difference between the two groups was the adequateness of the oral anticoagulants (OAC) that were administered where the paroxysmal AF group might not receive OAC at all. Therefore, to identify the patient with paroxysmal AF is challenging.

In general, the presence of AF doubles the mortality rate and increases the stroke rate to five times the level found in normal population[2]. On the other hand, a fifth of the people who suffer from ischemic stroke will have AF as a cause. However, in a recent study, patients with acute ischemic stroke

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and an unknown etiology represented about 25% of all cases of stroke. That group of patients was regarded as having a "cryptogenic stroke"[5]. Gladstone et al conducted a study of 572 patients with cryptogenic stroke and found that AF was detected five times more often in a 30-day cardiac event recorder group than in a 24-hour Holter-monitoring group. In addition, the cardiac event recorder group of patients were treated with OAC twice as often as those whose AF had not been detected[5]. Those findings raised our concern about subclinical AF (undetected asymptomatic paroxysmal AF) and the risk for ischemic stroke.

Nowadays, the technology for cardiovascular investigation and treatment is very advanced, and it encompasses permanent pacemaker devices. Dual-chamber pacemakers, which can detect arrhythmia in both the atrium and the ventricle using an intracardiac electrogram (EGM), especially in the right atrium, can detect the duration and frequency of atrial arrhythmias. These arrhythmias are reported in terms of their atrial tachycardia/atrial fibrillation burden (AT/AF burden) or as an atrial high-rate events (AHRE). This means that all patients with a dual-chamber pacemaker are, in effect, receiving self-continuous electrocardiogram (ECG) monitoring.

Recently, Healey et al reported a study of patients with a cardiac implantable electronic device (CIED) implantation who were divided into two groups, whether they had AHRE or not. The results showed a higher incidence of stroke in the AHRE group (accounting for 10% of all participant patients during the 3-month study period) than in the non-AHRE group (4.6% versus 1.7%, respectively)[6]. These data show the importance of AHRE detection, which may be an indicator of subclinical AF detection, as it may affect the management of the patients concerned.

The present study aimed to evaluate the prevalence of AHRE in patients who had undergone CIED implantation in the Thai population. The secondary outcome was to determine whether AHRE is associated with the risk of stroke in this population.

Materials and Methods

Study design and patient population

The authors conducted a retrospective, cohort, descriptive study of patients who had undergone any CIED implantation (including a permanent pacemaker, automated implantable cardioverter-defibrillator, and cardiac resynchronization therapy) at Siriraj Hospital, Thailand, between January 1, 2008 and December 31, 2014. The median follow-up time was 5.8 years.

The inclusion criteria included all patients who had undergone CIED implantation during the specified study period. The exclusion criteria were those patients who had been previously diagnosed with AF and/or had been prescribed OAC for any reason prior to their admission to hospital for the CIED implantation or who had inadequate data in their medical records.

The research was approved by the Ethics Committee for Human Research at the Faculty of Medicine, Mahidol University.

Data collection

The authors performed a retrospective chart review using the digital records held by Siriraj Hospital, Mahidol University, Bangkok. The review encompassed the demographic data (age and sex), underlying disease (hypertension, dyslipidemia, diabetes mellitus, coronary artery disease, cardiomyopathy, and prior stroke), CHA_2DS_2VASc score, drug used (statin, aspirin, and other antiplatelets), indication and type of CIED implantation, prevalence of stroke, type of stroke, survival, newly prescribed treatment, presence of mitral stenosis, and left ventricular ejection fraction.

An AHRE, which was classified as being present or absent, was defined as an atrial rate that was faster than 150 beats per minute and with a duration of more than six minutes, as revealed by a CIED interrogation. A stroke, which included a transient ischemic attack, was defined by the symptoms and/or neuroimaging.

The primary outcome was the prevalence of AHRE detected in CIED-implanted patients in our single-center study. The secondary outcome was the association between the detected AHRE and stroke.

Statistical analysis

All analyses were performed using IBM SPSS Statistics for Macintosh, version 23 (IBM Corp., Armonk, NY, USA). The normally distributed continuous variables were described as mean ± standard deviation (SD). The non-normally distributed continuous variables were reported as median with interquartile range (IQR). Student's t-test was used to compare normally distributed data, and the Mann-Whitney U test was used for non-normally distributed data. The categorical variables were presented as number of cases and percentage. The Chi-square or Fisher's exact test was used to determine whether a difference existed between groups. A p-value lower than 0.05 was considered as statistical significance. Stroke-free survival rates and overall survival rates in the presence or absence of AHRE, and stroke-

Table 1. Baseline characteristics related to the presence or absence of AHRE

	No AHRE (n = 114) n (%)	AHRE (n = 82) n (%)	p-value
Male	62 (54.4)	45 (54.9)	0.946
Age (years), Mean±SD	70.5±12.1	69.1±14.3	0.454
Hypertension	88 (77.2)	57 (69.5)	0.227
Dyslipidemia	71 (62.3)	58 (70.7)	0.219
DM	45 (39.5)	30 (36.6)	0.682
CAD	35 (30.7)	25 (30.5)	0.974
Cardiomyopathy	22 (19.3)	17 (20.7)	0.828
Prior stroke	3 (2.6)	5 (6.1)	0.283
CHA_2DS_2VASc score*, Median (P25 to P75)	3.5 (2.0 to 4.0)	3.0 (2.0 to 5.0)	0.842
Prior treatment			
Statin	79 (69.3)	56 (68.3)	0.881
ASA	62 (54.4)	45 (54.9)	0.946
Other antiplatelet	15 (13.2)	17 (20.7)	0.157
CIED indication			0.654
AV node disease	56 (49.1)	47 (57.3)	
Sinus node dysfunction	38 (33.3)	24 (29.3)	
Heart failure (CRT)	19 (16.7)	11 (13.4)	
Prevention of sudden cardiac death (AICD)	1 (0.9)	0 (0.0)	
Type of CIED			0.740
Dual-chamber pacemaker	94 (82.5)	71 (86.6)	
CRT	19 (16.7)	11 (13.4)	
AICD	1 (0.9)	0 (0.0)	
Echocardiographic data			
Mitral stenosis	1 (0.9)	0 (0.0)	1.000
LVEF (%), Mean±SD	60.4±21.3	57.9±19.4	0.436

AHRE=atrial high-rate events; AICD=automated implantable cardioverter-defibrillator; ASA=aspirin; AV=atrioventricular; CAD=coronary artery disease; CIED=cardiac implantable electronic device; CRT=cardiac resynchronization therapy; DM=diabetes mellitus; LVEF=left ventricular ejection fraction; SD=standard deviation

* The CHA_2DS_2VASc score is the score used to predict the stroke risk in AF patients. Its components are C=congestive heart failure; H=hypertension; A_2=age >75 years; D=diabetes mellitus; S_2=stroke or transient ischemic attack; V=vascular disease; A=age 65 to 75 years; and Sc=sex category (i.e., female sex). Each component present counted as 1 point, except for A_2 and S_2, which are each counted as 2 points.

free survival rates and overall survival rates for CHA_2DS_2VASc score were compared using log-rank test and presented by Kaplan-Meier survival curve.

Results

One hundred ninety-six patients, after excluding those with preexisting AF and/or on OAC, were included in this study. Regarding our primary outcome, the overall rate of AHRE in our CIED implantation patients was 82 out of 196 (41.8%). Table 1 shows the baseline characteristics related to the presence or absence of AHRE (group 1=no AHRE; group 2=AHRE present).

No significant differences were revealed in any of the parameters such as age, sex, underlying disease, CHA_2DS_2VASc score, previous medication, indication and type of CIED, presence of mitral stenosis, and left ventricular ejection fraction.

Regarding the secondary outcomes, and in keeping with the long duration of the follow-up period, 20 patients (10.2%) were lost to follow-up (four from the AHRE group, and 16 from the non-AHRE group). Stroke occurred in five out of the 78 patients from the AHRE group (6.4%), compared to one out of the 98 patients in the non-AHRE group (1.0%); however, there was no statistical significance (Table 2). As to the five ischemic stroke patients from the AHRE group, none had been prescribed with OAC prior to their stroke. The mortality rates were similar, with 18 deaths out of 77 patients in the AHRE group (23.4%),

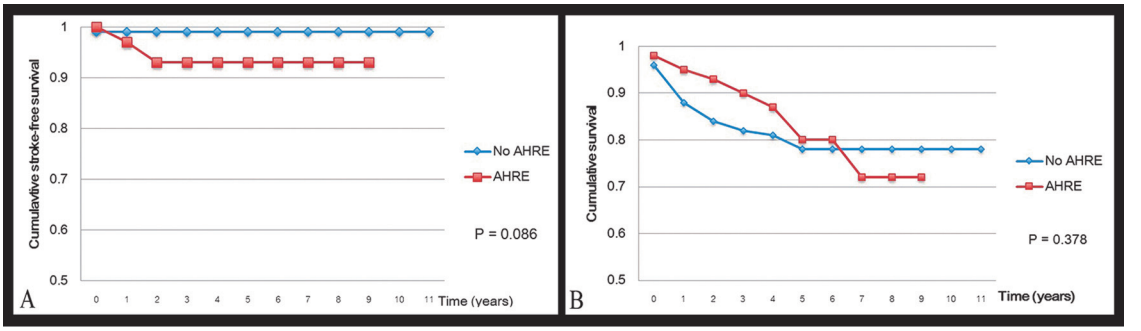

Figure 1. A) Stroke-free survival rates in the presence or absence of AHRE, AHRE, atrial high rate event. B) Overall survival rates in the presence or absence of AHRE, AHRE, atrial high rate event.

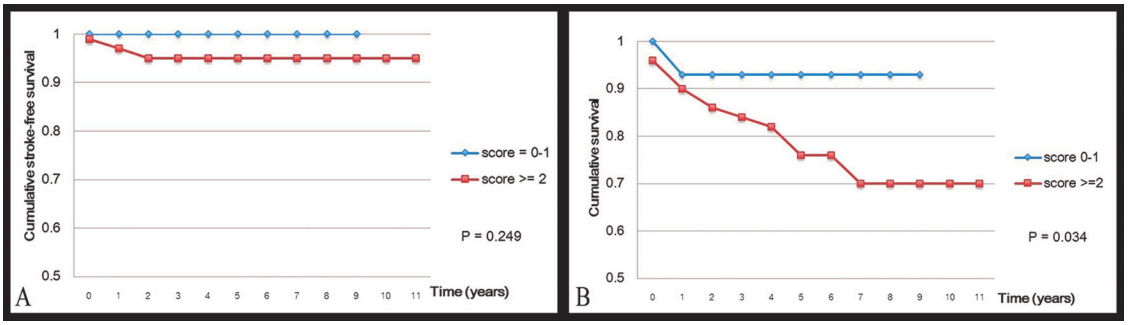

Figure 2. A) Stroke-free survival rates of the total population for CHA_2DS_2VASc scores of 0 to 1 and ≥2. B) Overall survival rates of the total population for CHA_2DS_2VASc scores of 0 to 1 and ≥2.

Table 2. Outcomes related to the presence or absence of AHRE

	No AHRE (n = 114) n (%)	AHRE (n = 82) n (%)	p-value
Lost to follow-up	16 (14.0)	4 (4.9)	0.037
Overall stroke	1/98 (1.0)	5/78 (6.4)	0.089
All causes of death	23/98 (23.5)	18/77* (23.4)	0.989

* One patient was lost to follow-up after the occurrence of the stroke

and 23 deaths out of 98 patients in the non-AHRE group (23.5%).

After AHRE was documented, 18 of the 82 AHRE patients (22%) were prescribed with OAC. Whereas 1 of the 114 non-AHRE patient (0.9%) was prescribed with OAC (p<0.001). Of those 18 patients in the AHRE group, 16 were prescribed with OAC as a primary prevention for stroke, and no one in this group developed stroke during follow-up. The other two patients were prescribed with OAC after stroke occurred as a secondary prevention.

The Kaplan-Meier curves at Figure 1A and 1B show the stroke-free survival and overall survival rates in the presence or absence of AHRE, while Figure 2A and 2B show the same survival rates of the total population for CHA_2DS_2VASc scores of 0 to 1 and more than 2. These data show that although the patients with AHRE tended to have a lower stroke-free survival rate and lower overall survival rate than patients without AHRE, there were no statistically significant differences (p=0.086 and 0.378, respectively). Patients with CHA_2DS_2VASc scores of 0 to 1 and 2 or more also had similar stroke-free survival results, but with no significant difference (p=0.249) (Figure 2A). However, those patients with a CHA_2DS_2VASc score of 2 or more had a significantly lower overall survival rate than patients with CHA_2DS_2VASc=0 to 1 (p=0.034) (Figure 2B).

Discussion

The authors present the findings of a study of 196 patients who received an implanted CIED during a 7-year period and who had a median follow-up time of 5.8 (4.5 to 7.4) years. The primary outcome of the

cohort was that AHRE occurred in 41.8% of the CIED-implanted patients. This proportion was higher than that reported in another study by Healey et al[6], which found that 34.6% of all patients experienced AHRE during the study period. A possible explanation for the difference in the rates could relate to the present study design, which was a retrospective chart review. This means that if a patient's intracardiac EGM data had been lost at some point, or if an EGM recording had never have been printed and stored in the medical record system, it will report only whether AHRE had been present or not. In addition, in the case of some of the patients in the present study, an EGM was not available to review to determine if a reported AHRE was compatible with AF or not. Consequently, a portion of the AHRE that had been reported in the patients' medical records may have represented an overestimate due to the presence of other arrhythmias, such as a supraventricular tachycardia or a sinus tachycardia with an atrial rate greater than 150 beats per minute. Regarding the secondary outcomes, a statistically significant association between AHRE and stroke was not evident, even though the proportion of stroke events was more than six times as high in the AHRE group than in the non-AHRE group (6.4% and 1.0%, respectively). This may be explained by the small scale of the events rate. Nevertheless, this result was concordant with the findings reported by Healey et al[6].

The only parameter that affected the survival rate in the present study was CHA_2DS_2VASc score, for which a score of 2 or more was associated with a lower overall survival rate than a score 0 to 1 (Figure 2B). This was not surprising as the higher the CHA_2DS_2VASc score, the worse is a patient's baseline health status. Furthermore, the median CHA_2DS_2VASc score in the present study was significantly higher for the group of patients who had had a stroke than for those who had not (5 and 3, respectively; p=0.031), which was expected.

Furthermore, the AHRE group had a higher incidence of OAC prescribed than the non-AHRE group (22% versus 0.9%; p<0.001), even though no definitive treatment recommendations are included in recently published guidelines. Regarding the warfarin prescribed for stroke prevention in patients who had AHRE (n = 78), there was no statistically significant difference in the stroke rates of the patients who had or had not been prescribed warfarin (0/16, 0.0% versus 5/62, 8.1%; p=0.577), despite none of the patients who had been prescribed warfarin for stroke prevention having experienced stroke. This, again, may be explained by the small event rate. This may be a topic for further study.

Limitation

There were a few limitations. For one thing, the authors could not conclusively specify which of the AHRE were "true" AF due to the retrospective nature of the study. Our threshold of 150 beats per minute for AHRE detection, which was lower than that previously reported[6], may lead to overestimation of the prevalence. Moreover, our cardiac device clinic routinely scheduled patients' follow-up periods every six months, which may have been too long for some minor symptoms to have been detected, such as that for transient ischemic attacks. That may have led to low event rates. Furthermore, many patients were lost to follow-up for a range of reasons (such as migration, death, or admission to another hospital). As Thailand does not yet have a nationwide medical healthcare system database, telephone calls were used for data collection, consequently, that may contribute to an inaccurate database profile. Finally, the present study included the cardiac resynchronization therapy (CRT)-implanted patients that may have worse prognosis when compared with those implanted with dual chamber pacemakers. However, the overall mortality was not significant different when compared between the non-AHRE group and AHRE group in the CRT implanted patients (4/19, 21% and 0/11, 0%, p=0.268).

On the other hand, as this study was one of the first Thai-population studies in this field, it provides much data for future research. A prospective trial that will address the limitations of the present study is planned.

Conclusion

The present study found that AHRE, which was assumed to be subclinical AF, was found in a substantial proportion (41.8%) of the Thai population study group who had been implanted with a dual-chamber CIED. Nevertheless, the study showed that there is no statistically significant association between either AHRE and stroke, or AHRE and the mortality rate.

What is already known on this topic?

The AHRE incidence had previously been reported as 34.6% by Healey et al, and patients with AHRE have a higher incidence of stroke than those without AHRE. However, there were no data for the Thai population. The authors believed that the results may differ from those reported for Caucasian subjects

because the Asian population has a higher incidence of stroke than that for Caucasians.

What this study adds?

The study presents a clear incidence of AHRE in the Thai population; however, the authors could not demonstrate a correlation between AHRE and stroke. The authors also raised the hypothesis of utilizing OAC for stroke prevention, although not statistically significant, the patients in AHRE group that prescribed with OAC tended to have less stroke events.

Conflicts of interest

The authors declare no conflict of interest.

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